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(54) Title: THERAPEUTIC MOLECULES (57) Abstract The present invention relates generally to therapeutic molecules. More particularly, the present invention provides therapeutic molecules capable of interacting with Interleukin-13 (IL-13) and to genetic sequences encoding these therapeutic molecules. The therapeutic molecules of the present invention are useful in modulating the action of IL-13 <i>in vivo</i> .		

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THERAPEUTIC MOLECULES

The present invention relates generally to therapeutic molecules. More particularly, the present invention provides therapeutic molecules capable of interacting with Interleukin-13 (IL-13) and
5 to genetic sequences encoding these therapeutic molecules. The therapeutic molecules of the present invention are useful in modulating the action of IL-13 *in vivo*.

Bibliographic details of the publications referred to by author in this specification are collected at the end of the description. Sequence Identity Numbers (SEQ ID NOs.) for the amino acid
10 sequences referred to in the specification are defined following the bibliography.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other
15 integer or group of integers.

The increasing sophistication of recombinant DNA technology is greatly facilitating research in the medical and allied health fields. A particularly important area of research is in the field of cytokines since these molecules are involved in a host of regulatory mechanisms including roles
20 in immune potentiation, cell differentiation and proliferation and in modulating haemopoietic potentiation activities.

One important cytokine is Interleukin-13 (IL-13) which is produced by activated T-cells and is involved in regulation of the immune response by, for example, inducing immunoglobulin class
25 switching to IgG1 and IgE isotypes and in inhibiting release of inflammatory mediators by macrophages. IL-13 is structurally related to another, functionally similar cytokine, interleukin 4 (IL-4) and both cytokines share common receptor components (Howard and Harada, 1994; McKenzie and Zurawski, 1994; Zurawski and deVries, 1994).

30 The IL-13 receptor α -chain (IL-13R α) has recently been cloned (Hilton *et al*, 1996). Analysis of IL-13R α together with other cloned receptors indicates that IL-13 may first bind IL-13R α and

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then recruit IL-4R α to form a high affinity receptor. IL-2R γ does not appear to play a central role in IL-13 receptor function, whereas in the case of IL-4, binding occurs initially with IL-4R α and this complex may interact with either IL-2R γ or IL-13R α to yield a high affinity receptor capable of signal transduction.

5

The pleiotropic properties of many cytokines such as IL-13 may cause difficulties during treatment regimes. It would be useful to administer IL-13 or a related cytokine to effect a particular response and then to administer a blocking agent to prevent further activity at the localised area. This is also important if the IL-13 administered is capable of inducing an adverse
10 immune response against itself or native IL-13. There are also a range of conditions aggravated by IL-13 such as allergic conditions. The ability to reduce IL-13 action would provide a valuable therapeutic tool in treating these conditions.

In work leading up to the present invention, a high affinity binding protein for IL-13 has been
15 identified in mammalian bodily fluid. The protein is functionally, structurally and antigenically distinct from cloned, soluble IL-13R α and acts as a potent antagonist of IL-13 action.

Accordingly, one aspect of the present invention provides an isolated proteinaceous molecule or a recombinant or synthetic form thereof capable of interacting with IL-13 or a related cytokine
20 with greater affinity than soluble IL-13R α .

The proteinaceous molecule may be a peptide, polypeptide or protein and may be naturally or non-naturally glycosylated or unglycosylated. Differential glycosylation patterns may be obtained depending on the host cell which synthesises the proteinaceous molecule. When a recombinant
25 form of the molecule is produced in prokaryotic cells, for example, the molecule would be substantially non-glycosylated. All forms of glycosylation including substantial absence of glycosylation of the subject proteinaceous molecule are encompassed by the present invention.

The proteinaceous molecule and the IL-13 may be derived from the same animal species (ie
30 homologous) or both molecules may be derived for different species (ie heterologous). Animal species contemplated by the present invention include but are not limited to humans, livestock

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animals (eg sheep, cattle, horses, donkeys, pigs, goats), laboratory test animals (eg rabbits, guinea pigs, rats, mice), companion animals (eg dogs, cats), and captive wild animals (eg foxes, deer, kangaroos and other marsupials, dingoes). Preferably, the proteinaceous molecule is from humans or murine animals.

5

The proteinaceous molecule of the present invention may be a naturally occurring molecule in isolated form or may be a functional derivative thereof. A "functional derivative" means that the molecule retains its ability to interact with IL-13 or a related cytokine or a derivative of IL-13. Derivatives contemplated by the present invention include mutants, fragments, parts, portions, truncated forms, fused forms, hybrid forms, homologues and analogues as well as glycosylation variants. All such forms are within the scope of the present invention and are encompassed by the terms "derivative" and "derivatives". The proteinaceous molecule of the present invention is hereinafter referred to as "IL-13 binding protein" (IL-13BP) which includes naturally occurring, recombinant, synthetic and derivative forms thereof.

15

Reference herein to "isolated" forms of IL-13BP includes reference to a biologically pure preparation of the molecule. Such a purified molecule has undergone at least one purification step from a mixture. Conveniently, a biologically pure preparation is a preparation containing at least about 1%, more particularly at least about 10%, even more particularly at least about 20%, still even more particularly greater than about 30%, eg. 40-50%, 60-70% or above of IL-13BP or its derivative as determined by, for example, weight, binding activity, antagonising ability, immunointeractivity or other convenient means.

Mutants include single or multiple amino acid substitutions, deletions and/or additions to the naturally occurring IL-13BP amino acid sequence.

Hybrid forms include but are not limited to hybrids between IL-13BP and IL-4BP which hybrid being capable of interacting with both IL-13 and IL-4. Accordingly, another aspect of the present invention provides a polypeptide having first and second portions wherein one of said first and second portions is IL-13BP or a functional derivative thereof and the other of said first and second portions is IL-4BP or a functional derivative thereof wherein said polypeptide is

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capable of modulating biological processes involving IL-13 and/or IL-4. In one embodiment, there is an amino acid spacer between said first and second portions. The spacer may range from one amino acid to 100 amino acids, more preferably between three amino acids and twenty amino acids and even more preferably between five and fifteen amino acids. The hybrid polypeptide
5 may not necessarily modulate equally IL-13 and IL-4 biological processes but may, for example, be 60-80% effective for IL-13 processes and only 20-50% effective for IL-4 processes or *vice versa*.

Another particularly preferred hybrid comprises IL-13BP or derivative forms thereof and IL-13
10 receptor α -chain (IL-13R α) or its derivatives. Such a hybrid may be particularly useful in modulating activities of related molecules such as, but not limited to, IL-13, IL-13BP, IL-13R α , IL-4, IL-4BP and IL-4 receptor α -chain (IL-4R α). The IL-13R α is disclosed in Hilton *et al*, 1996.

15 Still further hybrids include hybrids between IL-13BPs from different species. For example, a hybrid between all or a functional part of human and murine IL-13BPs.

Analogues of IL-13BP contemplated herein include, but are not limited to, modification to side chains, incorporating unnatural amino acids and/or their derivatives during peptide, polypeptide
20 or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde
25 followed by reduction with NaBH₄; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH₄.

30

The guanidine group of arginine residues may be modified by the formation of heterocyclic

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condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide.

5

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-
10 chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides.

15 Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

20

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of
25 amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 1.

Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with $n=1$ to $n=6$, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually
30 contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition,

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peptides can be conformationally constrained by, for example, incorporation of C α and N α -methylamino acids, introduction of double bonds between C α and C β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and
5 the N or C terminus.

These types of modifications may be important to stabilise IL-13BP if administered to an individual or for use as a diagnostic reagent.

10 The present invention further contemplates chemical analogues of IL-13BP capable of acting as antagonists or agonists of IL-13BP or which can act as functional analogues of IL-13BP which are capable of acting as antagonists of IL-13 activity. Chemical analogues may not necessarily be derived from IL-13BP but may share certain conformational similarities to the molecule as a whole or to its active site(s). Alternatively, chemical analogues may be specifically designed to
15 mimic certain physiochemical properties of IL-13BP. Chemical analogues may be chemically synthesised or may be detected following, for example, natural product screening.

TABLE 1

Non-conventional amino acid	Code	Non-conventional amino acid	Code
5 α -aminobutyric acid	Abu	L-N-methylalanine	Nmala
α -amino- α -methylbutyrate	Mgab	L-N-methylarginine	Nmarg
aminocyclopropane- carboxylate	Cpro	L-N-methylasparagine	Nmasn
		L-N-methylaspartic acid	Nmasp
10 aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl- carboxylate	Norb	L-N-methylglutamine	Nmgln
		L-N-methylglutamic acid	Nmglu
cyclohexylalanine		Chexa L-N-methylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
15 D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Das	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
20 D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
25 D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
30 D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva

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	D-tyrosine	Dtyr	α -methyl-aminoisobutyrate	Maib
	D-valine	Dval	α -methyl- γ -aminobutyrate	Mgab
	D- α -methylalanine	Dmala	α -methylcyclohexylalanine	Mchexa
	D- α -methylarginine	Dmarg	α -methylcyclopentylalanine	Mcpen
5	D- α -methylasparagine	Dmasn	α -methyl- α -naphthylalanine	Manap
	D- α -methylaspartate	Dmasp	α -methylpenicillamine	Mpen
	D- α -methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D- α -methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D- α -methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
10	D- α -methylisoleucine	Dmile	N-amino- α -methylbutyrate	Nmaabu
	D- α -methyllleucine	Dmleu	α -naphthylalanine	Anap
	D- α -methyllysine	Dmlys	N-benzylglycine	Nphe
	D- α -methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
	D- α -methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
15	D- α -methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
	D- α -methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
	D- α -methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D- α -methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D- α -methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
20	D- α -methyltyrosine	Dmtty	N-cyclodecylglycine	Ncdec
	D- α -methylvaline	Dmval	N-cyclododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
25	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl)glycine	Nser
30	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl)glycine	Nhis
	D-N-methyllleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp

	D-N-methyllysine	Dnmlys	N-methyl- γ -aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmt
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
5	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyl- α -naphthylalanine	Nmanap
10	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	γ -aminobutyric acid	Gabu	N-(<i>p</i> -hydroxyphenyl)glycine	Nhtyr
	L- <i>t</i> -butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
	L-ethylglycine	Etg	penicillamine	Pen
	L-homophenylalanine	Hphe	L- α -methylalanine	Mala
15	L- α -methylarginine	Marg	L- α -methylasparagine	Masn
	L- α -methylaspartate	Masp	L- α -methyl- <i>t</i> -butylglycine	Mtbug
	L- α -methylcysteine	Mcys	L-methylethylglycine	Metg
	L- α -methylglutamine	Mgln	L- α -methylglutamate	Mglu
	L- α -methylhistidine	Mhis	L- α -methylhomophenylalanine	Mhphe
20	L- α -methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L- α -methyllaucine	Mleu	L- α -methyllysine	Mlys
	L- α -methylmethionine	Mmet	L- α -methylnorleucine	Mnle
	L- α -methylnorvaline	Mnva	L- α -methylornithine	Morn
	L- α -methylphenylalanine	Mphe	L- α -methylproline	Mpro
25	L- α -methylserine	Mser	L- α -methylthreonine	Mthr
	L- α -methyltryptophan	Mtrp	L- α -methyltyrosine	Mtyr

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L- α -methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
N-(N-(2,2-diphenylethyl)	Nnbhm	N-(N-(3,3-diphenylpropyl)	Nnbhe
carbamylmethyl)glycine		carbamylmethyl)glycine	
1-carboxy-1-(2,2-diphenyl-	Nmbc		
5 ethylamino)cyclopropane			

In a particularly preferred embodiment, the interaction between IL-13BP and IL-13 results in antagonism of IL-13 activity. The antagonism may be from mild to substantial in relation to at least one property attributable to IL-13. For example, the antagonism may result in about 1-10% reduction or about 10-30% reduction or about 30-50% reduction or about 50-70% or greater (eg >90%) relative to at least one property attributable to IL-13 or a related cytokine. In a particularly preferred embodiment, IL-13BP binds to IL-13 with a greater than 50-fold higher affinity compared to IL-13R α .

15

Another aspect of the present invention contemplates a method for purifying IL-13BP or its derivatives or hybrid forms from a biological sample including body fluid or cell culture medium, said method comprising contacting said biological sample with immobilised IL-13 (or an IL-13/IL-4 hybrid) or a binding derivative thereof for a time and under conditions sufficient for a complex to form between said IL-13 (or IL-13/IL-4) and its binding protein, eluting said IL-13BP (or IL-13/IL-4) from the immobilised IL-13 (or IL-13/IL-4) and collecting said eluted IL-13BP.

Preferably, the eluate is subjected to further purification on an HPLC or equivalent chromatography.

Preferably, the HPLC or equivalent chromatographic purified samples are further purified or analysed on SDS-PAGE.

The IL-13BP is antigenically, structurally and functionally distinct from IL-13R α . IL-13BP is isolatable from biological fluid such as from urine or other excretable fluid, circulatory fluid

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such as from serum, whole blood, plasma or lymph fluid or respiratory fluid such as sputum, nasal secretion and saliva. The biological fluid may also comprise medium conditioned by human or animals cells, cell lines, organs and/or tissues. Preferably, the IL-13BP is isolatable from urine or serum.

5

Native soluble IL-13BP has an apparent molecular mass of approximately 40,000 to 60,000 daltons and more preferably about 55,000 \pm 5,000 daltons. Conveniently, the molecule weight may be determined by SDS-PAGE.

10 In a particularly preferred embodiment of the present invention, there is provided an isolated proteinaceous molecule comprising the following properties:

- (i) has a molecular weight in its native soluble form of from about 40,000 to about 60,000 daltons;
 - (ii) is isolatable in its native soluble form from urine or serum;
 - 15 (iii) is capable in its native soluble form of binding to IL-13 with greater affinity than IL-13R α ;
 - (iv) is antigenically and structurally distinct from IL-13R α ; and
 - (v) migrates as a single band on SDS-PAGE;
- or a derivative of said proteinaceous molecule.

20

Preferably, the proteinaceous molecule is an antagonist of at least one property attributable to IL-13.

Another aspect of the present invention provides an isolated IL-13BP comprising the amino
25 acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.

Still another aspect of the present invention provides an isolated IL-13BP comprising the amino
acid sequence EIKVNPPQDFEIXDPGLGYLYLQ [SEQ ID NO:13] or a derivative,
30 homologue or analogue thereof.

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Even yet another aspect of the present invention provides an isolated IL-13BP comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.

- 5 In yet a further aspect of the present invention provides an isolated IL-13BP comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGYYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

Yet another aspect of the present invention provides an isolated IL-13BP having an amino acid
10 sequence set forth in one of SEQ ID NO:6 or 7 or 8 (N-terminal sequence) or SEQ ID NO:10 or 11 or 12 (C-terminal sequence) or comprises at least about 50% similarity and more preferably at least about 60%, still more preferably at least about 75-80% similarity to at least one of SEQ ID NO:6 or 7 or 8 or 10 or 11 or 12.

- 15 Reference herein to N- or C-terminal sequences include reference to a region at the N- or C-terminal portion of the molecule. It does not, for example, imply any limitation as to including the initiating methione although such a methione may be included in said N-terminal sequence.

In still yet another aspect of the present invention, there is provided an isolated human IL-13BP
20 having the amino acid sequence corresponding to SEQ ID NO:20 or a sequence having at least about 50% similarity thereto.

Another aspect of the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides which encodes or is complementary to a sequence which encodes a
25 proteinaceous molecule capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13R α .

More particularly, the present invention contemplates a nucleic acid molecule comprising a sequence of nucleotides which encodes or is complementary to a sequence which encodes a
30 proteinaceous molecule comprising the following properties:

- (i) has a molecular mass in its native soluble form of from about 40,000 to about

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60,000 daltons;

- (ii) is isolatable in its native soluble form from urine or serum;
 - (iii) is capable in its native soluble form of binding to IL-13 with greater affinity than IL-13R α ;
 - 5 (iv) is antigenically and structurally distinct from IL-13R α ; and
 - (v) migrates as a single band on SDS-PAGE;
- or a derivative of said proteinaceous molecule.

Sub paragraph (i) above is not intended to limit the molecule of the present invention to a
10 soluble form of from 40,000 to 60,000 daltons but rather the native soluble form of the molecule would have these characteristics.

Preferably, the proteinaceous molecule is an antagonist of at least one property attributable to IL-13.

15

Preferably, the nucleic acid molecule is capable of hybridising with low stringency conditions to one or both of 5' ATGGCTTTCGTTTGCTTGGCTATC3' [SEQ ID NO:2] and/or 5'CAACATTCGCAAGAAAAATTCAGTTTATT3' [SEQ ID NO:3] or complementary forms thereof. Preferably, the nucleic acid molecule encodes a proteinaceous molecule comprising
20 the amino acid sequence set forth in SEQ ID NO:1 or 13 or 21 or 22. Alternatively or in addition, a preferred nucleic acid molecule encodes an N-terminal amino acid sequence as set forth in one of SEQ ID NO:6 or 7 or 8 or a C-terminal amino acid sequence as set forth in SEQ ID NO:10 or 11 or 12.

25 In a particularly preferred embodiment, the amino acid sequence is as set forth in SEQ ID NO:19.

Even more preferably the nucleic acid molecule comprises the nucleotide sequence set forth in SEQ ID NO:5 and/or SEQ ID NO:9 and/or 19 or a nucleic acid molecule capable of hybridizing
30 under low stringency conditions at 42°C and/or is a nucleic acid molecule having at least about 50% nucleotide sequence similarity thereto.

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Preferred similarities include at least about 60%, at least about 75% and at least about 85-90% to all or preferably to at least 20 contiguous base pairs of the nucleotide sequences set forth in SEQ ID NO:5 and/or SEQ ID NO:9 and/or SEQ ID NO:19.

5 Reference herein to a low stringency at 42°C includes and encompasses from at least about 1% v/v to at least about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v
10 formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions.

15

The nucleic acid molecule may be genomic DNA in isolated form or cDNA or mRNA or hybrid forms thereof. The nucleotide sequence may correspond to the native genomic sequence or the cDNA sequence or may comprise single or multiple nucleotide substitutions, deletions and/or additions.

20

The nucleic acid molecules are generally in isolated form but may also be integrated into or ligated to or otherwise fused or associated with other genetic molecules such as vector molecules and in particular expression vector molecules. Vectors and expression vectors are generally capable of replication and, if applicable, expression in one or both of a prokaryotic
25 cell or a eukaryotic cell. Preferably, prokaryotic cells include *E. coli*, *Bacillus sp* and *Pseudomonas sp*. Preferred eukaryotic cells include yeast, fungal, mammalian and insect cells.

Accordingly, another aspect of the present invention contemplates a genetic construct comprising a vector portion and a mammalian IL-13BP gene portion or a derivative thereof,
30 which IL-13BP gene portion encodes an IL-13BP peptide, polypeptide or protein or a functional or immunologically interactive derivative thereof capable of binding to IL-13.

- 15 -

Preferably, the IL-13BP gene portion of the genetic construct is operably linked to a promoter, such as on the vector, such that said promoter is capable of directing expression of said IL-13BP gene portion in an appropriate cell.

- 5 In addition, the IL-13BP gene portion of the genetic construct may comprise all or part of the gene fused to another genetic sequence such as a nucleotide sequence encoding glutathione-S-transferase or part thereof.

The IL-13BP of the present invention or its derivatives are contemplated to be useful, *inter*
10 *alia*, in the antagonism of at least one IL-13 activity. This may be important for IL-13 mediated conditions such as certain allergic conditions such as asthma or to inactivate locally administered IL-13 after IL-13 treatment.

Accordingly, another aspect of the present invention contemplates a method of treatment
15 comprising administering to a patient an IL-13 antagonising effective amount of an IL-13BP or its derivative for a time and under conditions sufficient to antagonise at least one property of IL-13. For example, IL-13 may have the effect of increasing the level of receptors for rhinoviruses. Antagonising IL-13 would have the effect of reducing adverse rhinovirus interaction such as interaction leading to asthma.

20

In one embodiment, the treatment is for an allergic response or allergic reaction.

In an alternative embodiment, there may be circumstances where IL-13BP complexes with IL-13 can, in fact, enhance cytokine mediated processes. Accordingly, this embodiment is
25 encompassed by the present invention.

The present invention contemplates, therefore, a pharmaceutical composition comprising IL-13BP or a derivative thereof or a modulator of IL-13BP gene expression or IL-13BP activity and one or more pharmaceutically acceptable carriers and/or diluents. These components are
30 referred to as the "active ingredients".

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The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful

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compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 μg and 2000 mg of active compound. Alternative dosage amounts include from about 1 μg to about 1000 mg, from about 10 μg to above 800 mg and from about 5 20 μg to about 500 mg.

The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter. A binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; 10 a lubricant such as magnesium stearate; and a sweetening agent such a sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules 15 may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release 20 preparations and formulations.

The present invention also extends to forms suitable for topical application such as creams, lotions and gels.

25 Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active 30 ingredients can also be incorporated into the compositions.

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It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from 0.5 μ g to about 2000 mg. Expressed in proportions, the active compound is generally present in from about 0.5 μ g to about 2000 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

The effective amount of the active ingredient may be as defined above but must be in an amount effective to have the desired effect. Conveniently, this may be expressed as an amount per kilogram (kg) body weight and includes from about 10 ng to about 2000 mg/kg body weight, about 100 ng to about 1000 ng/kg body weight and about 1-10 μ g to above 500 ng/kg body weight.

25

The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating IL-13BP gene expression or IL-13BP activity. The vector may, for example, be a viral vector.

30

Still another aspect of the present invention is directed to antibodies to IL-13BP and its

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derivatives. These antibodies may be directed to soluble IL-13BP or cell surface bound IL-13BP. Antibodies and in particular antibodies directed to the cell surface bound IL-13BP may function as antagonists. The antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to IL-13BP or may be specifically raised to IL-13BP or
5 derivatives thereof. The antibodies may also be anti-idiotypic antibodies to the active site of IL-13BP. IL-13BP or its derivatives may first need to be associated with a carrier molecule in order to generate the antibodies.

The subject antibodies and/or IL-13BP or its derivatives of the present invention are particularly
10 useful as therapeutic or diagnostic agents.

For example, IL-13BP and its derivatives can be used to screen for naturally occurring antibodies to IL-13BP. These may occur, for example in some autoimmune diseases. Alternatively, specific antibodies can be used to screen for IL-13BP. Techniques for such
15 assays are well known in the art and include, for example, sandwich assays and ELISA. Knowledge of IL-13BP levels may be important for diagnosis of certain disease conditions associated with IL-13. The IL-13BP may also be used to assay for IL-13 directly or via antibodies.

20 Antibodies to IL-13BP of the present invention may be monoclonal or polyclonal. Alternatively, fragments of antibodies may be used such as Fab fragments. Furthermore, the present invention extends to recombinant and synthetic antibodies and to antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies. The antibodies of this aspect of the present invention are particularly useful for immunotherapy and
25 may also be used as a diagnostic tool for assessing, for example, apoptosis or monitoring the program of a therapeutic regimen.

For example, specific antibodies can be used to screen for IL-13BP proteins. The latter would be important, for example, as a means for screening for levels of IL-13BP in a cell extract or
30 other biological fluid or purifying IL-13BP made by recombinant means from culture supernatant fluid. Techniques for the assays contemplated herein are known in the art and

- 20 -

include, for example, sandwich assays and ELISA.

It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies
5 discussed above. Both the first and second antibodies may be used in detection assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of IL-13BP.

Both polyclonal and monoclonal antibodies are obtainable by immunization with the enzyme
10 or protein and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively easily prepared by injection of a suitable laboratory animal with an effective amount of IL-13BP, or antigenic parts thereof, collecting serum from the animal, and isolating specific sera by any of the known immunoabsorbent techniques. Although antibodies produced by this method are
15 utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation
20 of hybridoma cell lines for monoclonal antibody production derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation can be done by techniques which are well known to those who are skilled in the art.

Another aspect of the present invention contemplates a method for detecting IL-13BP in a
25 biological sample from a subject said method comprising contacting said biological sample with an antibody specific for IL-13BP or its derivatives or homologues for a time and under conditions sufficient for an antibody-IL-13BP complex to form, and then detecting said complex.

30 The presence of IL-13BP may be detected in a number of ways such as by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by

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reference to US Patent Nos. 4,016,043, 4,424,279 and 4,018,653. These, of course, include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labelled antibody to a target.

5

Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate and the sample to be tested brought
10 into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labelled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labelled antibody. Any unreacted material is washed away, and the presence of the
15 antigen is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled
20 in the art, including any minor variations as will be readily apparent. In accordance with the present invention the sample is one which might contain IL-13BP including cell extract, tissue biopsy or possibly serum, saliva, mucosal secretions, lymph, tissue fluid and respiratory fluid. The sample is, therefore, generally a biological sample comprising biological fluid but also extends to fermentation fluid and supernatant fluid such as from a cell culture.

25

In the typical forward sandwich assay, a first antibody having specificity for the IL-13BP or antigenic parts thereof, is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports
30 may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally

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consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or overnight if more convenient) and under suitable conditions (from about room temperature to about 40°C, eg. 25-37°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

10

An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

Another particularly useful alternative is to use IL-13 or a hybrid form thereof (eg. IL-13/IL-4) immobilised to a solid support to bind to IL-13BP and then to use an antibody to IL-13BP to detect binding to the immobilised IL-13. The antibody may be labelled or an anti-immunoglobulin or an anti-immunoglobulin antibody labelled with a reporter molecule could be used.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

30

In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody,

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generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the
5 specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable colour change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labelled antibody is added to the first antibody hapten complex, allowed to bind, and
10 then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample. "Reporter molecule" also extends to use of cell agglutination or
15 inhibition of agglutination such as red blood cells on latex beads, and the like.

Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light
20 energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest.
25 Immunofluorescence and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

The present invention also contemplates genetic assays such as involving PCR analysis to detect
30 IL-13BP gene or its derivatives. Alternative methods or methods used in conjunction include direct nucleotide sequencing or mutation scanning such as single stranded conformation

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polymorphisms analysis (SSCP) as specific oligonucleotide hybridisation, as methods such as direct protein truncation tests.

The present invention also extends to immobilised IL-13 or derivatives thereof useful in the
5 purification of IL-13BP. Biological fluid is contacted with the immobilised IL-13 for a time and under conditions for a IL-13-IL-13BP complex to form. The IL-13BP is then eluted from the immobilised IL-13 and subjected to further purification steps.

A further aspect of the present invention contemplates an isolated polypeptide comprising an
10 amino acid sequence as set forth in SEQ ID NO:1 or 13 or 21 or 22 or an amino acid sequence set forth in SEQ ID NO:6 or 7 or 8 or 10 or 11 or 12 or 20 or having at least about 30% similarity to any one or more thereof. Preferred percentage similarities include at least about 40-50%, more preferably at least about 60-70%, and even more preferably at least about 80-90% or above. The polypeptide of this aspect of the present invention preferably has IL-13BP
15 properties or is a derivative thereof or is a hybrid form thereof.

The present invention further contemplates knockout animals such as mice or other murine species for the IL-13BP gene including homozygous and heterozygous knockout animals. Such animals provide a particularly useful live *in vivo* model for studying the effects of IL-13BP as
20 well as screening for agents capable of acting as agonists or antagonists of IL-13BP.

According to this embodiment there is provided a transgenic animal comprising a mutation in at least one allele of the gene encoding IL-13BP. Additionally, the present invention provides a transgenic animal comprising a mutation in two alleles of the gene encoding IL-13BP.
25 Preferably, the transgenic animal is a murine animal such as a mouse or rat.

The present invention is further described by the following non-limiting Figures and Examples.

In the Figures:

30

Figure 1 is a graphical representation of IL-13 binding to IL-13BP in mouse urine and serum

- 25 -

and soluble IL-13R α by gel filtration chromatography. The gel filtration column was equilibrated and run in TBS at 0.5 ml/min as described in the Examples. Panel A: 125 I-IL-13 alone (20,000 cpm); Panels C, E and G: 125 I-IL-13 (20,000 cpm) + 100 μ l DBA/2J mouse serum or in the presence of either 1 μ g/ml unlabelled IL-13 or IL-4, respectively; Panel B: 125 I-IL-13 alone (50,000 cpm); Panels D, F and H: 125 I-IL-13 (50,000 cpm) + 100 μ l NodL $^{+}$ /Jax mouse urine or in the presence of either 1 μ g/ml unlabelled IL-13 or IL-4, respectively.

Figure 2 is a graphical representation of 125 I-IL-13 binding to soluble IL-13R α and IL-13BP by gel filtration chromatography. Panel A: 125 I-IL-13 (50,000 cpm) + 10 μ g/ml soluble IL-13R α ; Panel B: 125 I-IL-13 (50,000 cpm) + 10 μ g/ml soluble IL-13R α + 0.5 μ g/ml soluble IL-4R α .

Figure 3 is a graphical representation showing a comparison of the ability of IL-13BP and soluble IL-13R α to inhibit the binding of IL-13 to its cell surface receptor. 10^5 cpm of 125 I-IL-13 and 125 I-GM-CSF were incubated for 40 min at 4°C with indicated dilution of partially purified urinary IL-13BP (A) or with the indicated concentration of soluble IL-13R α (B). The labelled ligand and the soluble IL-13R α or IL-13BP were then added to 50 μ l of medium containing 1.5×10^6 peritoneal cells from a GM-CSF transgenic mouse. Incubation was continued for a further 2 hr at 4°C before cell-associated and free 125 I-IL-13 or 125 I-GM-CSF were separated by centrifugation of cells through 200 μ l of foetal calf serum. The resulting cell pellets and supernatants were then counted in a γ -counter and specific binding was calculated as the difference between the 125 I-ligand bound in the absence and presence of the unlabelled competitor, in turn this was expressed as a percentage of that observed in the absence of either soluble IL-13R α or IL-13BP(●). As a control both soluble IL-13R α and IL-13BP showed no inhibition of 125 I-GM-CSF binding (O) to peritoneal cells.

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The following single and three letter abbreviations are used for amino acid residues:

5	Amino Acid	Three-letter	One-letter
		Abbreviation	Symbol
	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
10	Aspartic acid	Asp	D
	Cysteine	Cys	C
	Glutamine	Gln	Q
	Glutamic acid	Glu	E
	Glycine	Gly	G
15	Histidine	His	H
	Isoleucine	Ile	I
	Leucine	Leu	L
	Lysine	Lys	K
	Methionine	Met	M
20	Phenylalanine	Phe	F
	Proline	Pro	P
	Serine	Ser	S
	Threonine	Thr	T
	Tryptophan	Trp	W
25	Tyrosine	Tyr	Y
	Valine	Val	V
	Any residue	Xaa	X

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SUMMARY OF SEQ ID NOS.

SEQUENCE	SEQ ID NOs:
Amino acid sequence of N-terminal IL-13BP [generic]	1
Oligonucleotide capable of hybridising to human IL-13BP DNA (or complementary form thereof)	2
Oligonucleotide capable of hybridising to human IL-13BP DNA (or complementary form thereof)	3
FLAG peptide	4
Nucleotide sequence of N-terminal region of human IL-13BP (R52795)	5
Amino acid sequence of N-terminal region of human IL-13 BP	6
Amino acid sequence of N-terminal region of human IL-13 BP	7
Amino acid sequence of N-terminal region of human IL-13 BP	8
Nucleotide sequence of C-terminal region of human IL-13BP (R52796)	9
Amino acid sequence of C-terminal region of human IL-13BP	10
Amino acid sequence of C-terminal region of human IL-13BP	11
Amino acid sequence of C-terminal region of human IL-13BP	12
Amino acid sequence of N-terminal region of IL-13BP [partially generic]	13
Putative signal sequence in human IL-13BP	14
Oligonucleotide primers for PCR cloning of human IL-13BP	15
Oligonucleotide primers for PCR cloning of human IL-13BP	16
Nucleotide sequence of construct containing human IL-13BP cDNA	17
Amino acid sequence of SEQ ID NO:17	18
Nucleotide sequence of human IL-13BP	19
Amino acid sequence of human IL-13BP	20
Amino acid sequence of N-terminal IL-13BP [murine]	21
Amino acid sequence of N-terminal IL-13BP [human]	22

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EXAMPLE 1**REAGENTS**

Recombinant murine IL-13 was produced as a FLAG-tagged protein in *Pichia pastoris*.
5 Recombinant mouse IL-4 were purchased from R & D Systems. Recombinant soluble mouse IL-4R α was from Genzyme. N-Glycosidase F and protease V8 (sequencing grade) were obtained from Boehringer. BS³ (Bis (Sulfosuccinimidyl) suberate) was from Pierce. FLAG peptide (DYKDDDDK [SEQ ID NO:4]) and anti-FLAG M2 affinity gel were purchased from Scientific Imaging Systems. Soluble mouse IL-13 receptor α -chain (IL-13R α) which was N-
10 terminally-tagged with a FLAG epitope was expressed in CHO cells and purified from CHO cell-conditioned medium on an anti-FLAG M2 affinity column by affinity elution with free FLAG peptide. Anti-IL-13R α polyclonal antiserum was prepared by injecting purified soluble IL-13R α into rabbits which were bled after 3 months.

15

EXAMPLE 2**GEL FILTRATION CHROMATOGRAPHY**

Aliquots of samples were incubated with ¹²⁵I-IL-13 in the presence or absence of a competitor for at least 30 min at 4°C in a final volume of 200 μ l. The mixtures were applied to a Superdex
20 200 10/30 column (Pharmacia), equilibrated in 20 mM Tris-buffered saline, pH 7.0, containing 0.02% (v/v) Tween-20 and 0.02% (w/v) sodium azide. Samples were eluted with TBS at a flow rate of 0.5 ml/min, and 0.5-ml fractions were collected and counted in a γ -counter.

25

EXAMPLE 3**CROSSLINKING ASSAY**

Aliquots of 10- to 20-fold concentrated mouse urine were incubated with ¹²⁵I-IL-13 or ¹²⁵I-IL-4 in the presence or absence of a competitor in a final volume of 20 μ l for at least 30 min at 40°C. Then 5 μ l of a 12 mM BS³ solution in PBS containing 0.02% (v/v) Tween-20 was added and
30 the mixtures were incubated for 30 min at 4°C. Samples were mixed with 8 μ l of four-time concentrated SDS sample buffer and analysed by 13% (w/v) SDS/PAGE under non-reducing

conditions. The gels were dried and visualised by either autoradiography or PhosphorImager.

EXAMPLE 4

¹²⁵I-IL-13 SATURATION BINDING ASSAY

5

Binding of ¹²⁵I-IL-13 to COS-7 cells expressing IL-13R α was performed as previously described (Hilton *et al*, 1996). Binding of ¹²⁵I-IL-13 to soluble proteins in mouse serum and urine was determined by a gel filtration-based assay using Sephadex G-50 minicolumns (Nick column, Pharmacia) to separate free from bound ligand. Briefly, 50 μ l of serum or 90 μ l of
10 urine per tube was incubated for at least 30 min at 4°C with different amounts of ¹²⁵I-IL-13 in a final volume of 100 μ l. The mixtures were applied to 1.2 ml Sephadex G-50 columns previously washed with 20 mM Tris-buffered saline, pH 7.0, containing 0.02% (v/v) Tween-20 and 0.02% (w/v) sodium azide. After washing the columns with 350 μ l of column buffer, bound ¹²⁵I-IL-13 was eluted with 300 μ l of buffer, whereas free ¹²⁵I-IL-13 was eluted with 600
15 μ l of buffer. Specific binding was calculated by subtracting the cpm bound in the presence of 0.5 μ g/ml unlabelled IL-13 (nonspecific binding) from the cpm bound in its absence (total binding). Scatchard analyses of saturation binding isotherms were performed using the curve-fitting program Ligand (McPherson, 1985; Munson and Rodbard, 1980).

20

EXAMPLE 5

DEGLYCOSYLATION AND V8 DIGESTION

After SDS/PAGE, the gel, which contained ¹²⁵I-IL-13 crosslinked to either IL-13BP from mouse urine or purified soluble IL-13R α , was sliced according to pre-stained molecular weight
25 markers. The gel pieces were added with 10 μ l of Milli-Q water and 15 μ l of 0.1 M sodium phosphate buffer (pH 7.0) containing 10 mM EDTA, 0.1% (w/v) SDS, 0.01% (v/v) β -mercaptoethanol and minced into small pieces with a pair of tweezers. Then 15 μ l of 0.1 M sodium phosphate buffer (pH 7.0) containing 10 mM EDTA was added to the minced-gel mixtures. After 1 hr incubation at 37°C, the mixtures were heated for 1 min at 95°C, cooled
30 down, 4 μ l of 10% v/v β -octylglucoside added, and treated with N-glycosidase F (0.5 unit in 2.5 μ l) overnight at 37°C to complete the deglycosylation. The deglycosylated sample

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mixtures were then centrifuged and the gel pieces removed. The recovered liquid portions of the deglycosylated samples were further digested with protease V8 at concentrations ranging from 5 to 60 $\mu\text{g/ml}$ for 3 hr at 37°C. The samples were analysed by a 15% (w/v) SDS/PAGE under non-reducing conditions.

5

EXAMPLE 6

IMMUNOPRECIPITATION

Aliquots of 10-fold concentrated mouse urine or 3 $\mu\text{g/ml}$ purified soluble IL-13R α were
10 incubated with ^{125}I -IL-13 in the presence or absence of 0.5 $\mu\text{g/ml}$ unlabelled IL-13 and
crosslinking was then performed as described above. The crosslinking reaction was terminated
by adding 1M Tris-HCl buffer (pH 7.5) to a final concentration of 40 mM. The crosslinked
samples were then mixed with 1:50 diluted control rabbit serum or anti-IL-13R α antiserum
which had been pre-incubated with or without FLAG peptide at a concentration of 100 $\mu\text{g/ml}$
15 in order to eliminate false immunoreaction with potential anti-FLAG antibody in the anti-IL-
13R α polyclonal antiserum. After 30-min incubation at 4°C, the mixtures were added with 40
 μl of 50% (v/v) protein G-Sepharose gel slurry (Pharmacia) and incubated for 30 min at 4°C.
The samples were centrifuged and the protein G-Sepharose beads were washed 3 x 0.5 ml PBS,
mixed with 40 μl of two-time concentrated SDS sample buffer and heated for 2 min at 95°C.
20 The supernatants were then analysed by a 13% (w/v) SDS/PAGE under non-reducing
conditions.

EXAMPLE 7

PRODUCTION AND PREPARATION OF mIL-13 AFFINITY SUPPORT

25

Mouse IL-13 was produced as a N-terminally FLAG-tagged fusion protein in *Pichia pastoris*
and applied to an anti-FLAG antibody (M2) affinity column, non-binding proteins were washed
from the column with phosphate-buffered saline containing 0.02% (v/v) Tween 20 after which
the proteins that bound to the column, including the FLAG-tagged IL-13, were eluted with free
30 FLAG peptide. The IL-13 was further purified by RP-HPLC. To prepare mIL-13 affinity
support, the FLAG-tagged mIL-13 was first coupled to anti-FLAG antibody M2 affinity beads

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(Kodak) and then covalently linked to the M2 beads by the chemical cross-linker, BS³ (Pierce).

EXAMPLE 8

PURIFICATION OF mIL-13 BINDING PROTEIN

5

100 ml of concentrated mouse urine was incubated with mIL-13 affinity beads for 2 hr at room temperature. After removing unbound protein by centrifugation, the mIL-13 affinity beads were washed extensively with phosphate-buffered saline, pH 7.0, containing 0.02% (v/v) Tween-20 and 0.02% (w/v) sodium azide. The bound protein was eluted with Actisep elution medium
10 (Sterogenes Bioseparations). The eluates containing the active IL-13 binding protein was loaded onto a C8 reversed-phase HPLC column to achieve further purification. Aliquots of fractions eluted from the RP-HPLC column was further analysed by SDS-PAGE, after which the gel was silver stained. Fractions were also analysed for their ability to bind to ¹²⁵I-IL-13 using the cross-linking protocol described above.

15

EXAMPLE 9

IDENTIFICATION OF IL-13BP

Given the expression of transmembrane and secreted forms of many members of the
20 haemopoietin receptor family from alternatively spliced transcripts, the inventors sought to determine if this was the case for the IL-13R α .

Using an analytical gel filtration-based assay, mouse serum and urine were examined for the presence of an IL-13 binding protein (referred to hereon as "IL-13BP"). Analytical gel
25 filtration chromatography of ¹²⁵I-IL-13 alone resulted in elution of radioactivity in fractions 35 to 39 (Figures 1A and 1B). Prior addition of mouse serum or mouse urine to the ¹²⁵I-IL-13 resulted in the presence of an addition peak of ¹²⁵I-IL-13 eluting earlier in fractions 27 to 30 (Figure 1C and 1D), this higher molecular weight peak was competed for by the addition of an excess of unlabelled IL-13 but not unlabelled IL-4, demonstrating that the interaction with IL-
30 13BP was specific (Figures 1E and 1F).

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In contrast to crude mouse urine, purified soluble IL-13R α , appeared unable to bind IL-13 as assessed by gel filtration chromatography (Figure 2A). The very low affinity of IL-13 for the IL-13R α (Hilton *et al*, 1996) suggested that the serum and urine IL-13BP were either distinct from the IL-13R α or contained other components in addition to IL-13R α . One candidate for
5 a protein capable of interaction with IL-13R α to generate a high affinity IL-3 receptor is the IL-4R α . The presence of IL-4R α in urine and serum has been described in a number of previous studies. This result was confirmed by gel filtration chromatography, however, despite the presence of an IL-4 binding protein in urine and serum, addition of purified IL-4R α to purified IL-13R α did not recapitulate the properties of the IL-13BP found in serum and urine as
10 assessed by gel filtration chromatography (Figure 2B).

In order to assess the size of the IL-13BP and its relationship to the IL-4 binding protein, mouse urine was fractionated on a preparative gel filtration column. Aliquots from each fraction were then mixed with 125 I-IL-13 or 125 I-IL-4 in the presence or absence of an excess
15 of unlabelled IL-4 or IL-13 and subject to cross-linking using the bi-functional reagent dimethyl succinimydyl suberate (DSS). The products of the cross-linking reaction were then resolved by SDS-polyacrylamide electrophoresis and visualised by autoradiography. Cross-linking of 125 I-IL-13 to unfractionated mouse urine revealed the presence of a major band that electrophoresed with an apparent molecular mass of approximately 70,000 daltons. Given 125 I-
20 IL-13 electrophoreses with an apparent molecular mass of 15,000 daltons, this would suggest the IL-13BP has an apparent molecular mass of 55,000 daltons. Cross-linking to the IL-13BP was specific since it was in competition with unlabelled IL-13 but not IL-4. The Mr 55,000 dalton IL-13BP eluted from the gel filtration column in fractions 27 to 29, consistent with its molecular weight estimated from the cross-linking experiment. Additional non-specific lower
25 molecular radioactive products were also observed in the cross-linking studies with 125 I-IL-13. One of these eluted from the gel filtration column in fractions 29 and 30, after the Mr 55,000 dalton IL-13BP, but in a similar position to an IL-4 binding protein. Cross-linking of 125 I-IL-4 to the IL-4 binding protein resulted in a species migrating with an apparent molecular weight of approximately 55,000 daltons, suggesting the binding protein itself had a molecular mass of
30 35,000 daltons.

- 33 -

The specificity of the Mr 55,000 dalton IL-13BP to purified receptor components was examined further using cross-linking. Although binding of ^{125}I -IL-13 to purified IL-13R α was not detected by gel filtration chromatography, an interaction was observed using cross-linking. Consistent with previous studies (Hilton *et al*, 1996), this interaction was competed for by 5 unlabelled IL-13 but not unlabelled IL-4. Cross-linking studies were performed using ^{125}I -IL-13 and purified IL-4R α and a product with an apparent molecular weight 55,000 was observed. Surprisingly, cross-linking of ^{125}I -IL-13 to IL-4R α was in competition with unlabelled IL-4 but not IL-13. Combining purified IL-13R α and IL-4R α with ^{125}I -IL-13 resulted in the generation of species similar in molecular weight and specificity to reactions containing each receptor 10 alone. No higher molecular weight complexes were observed suggesting that formation of ternary IL-13/IL-13R α /IL-4R α complexes or their capture with the cross-linker occurred inefficiently in solution, even at high concentrations of each component. Consistent with the initial experiment, crude mouse urine contained a major Mr 55,000 dalton IL-13BP. Cross-linking of ^{125}I -IL-13 to this species was in competition with unlabelled IL-13 but not unlabelled 15 IL-4. The lower molecular species observed in our initial experiment, was again observed. As before, cross-linking of ^{125}I -IL-13 to this protein was not in competition with unlabelled IL-13; however, like cross-linking ^{125}I -IL-13 to purified IL-4R α , cross-linking to this protein was competed for by IL-4. Although the addition of purified IL-4R α to purified IL-13R α did not alter the pattern of cross-linking observed to either component alone, the inventors sought to 20 determine whether purified IL-4R α could interact with partially purified 50,000 Mr IL-13BP from mouse urine. As with the purified receptor components, no effect of adding IL-4R α was observed.

While interaction between IL-13 and both purified soluble IL-13R α and the Mr 55,000 dalton 25 IL-13BP was demonstratable by cross-linking, only the interaction with the IL-13BP was detectable using analytical gel filtration chromatography. These results suggested that the affinity of IL-13 for the IL-13BP was higher than for soluble IL-13R α . In order to test this formally, saturation binding experiments were performed. Scatchard transformations reveal that, consistent with previous studies (Hilton *et al*, 1996), the affinity of IL-13 for the IL-13R α 30 expressed by CHO cells was approximately 10 nM. However, the affinity of IL-13 for serum and urinary IL-13BP was 100 to 300-fold higher, ranging from 20 to 90 pM. The difference

- 34 -

in affinity was confirmed in cross-linking experiments in which ^{125}I -IL-13 was mixed with increasing concentrations of unlabelled IL-13 prior to cross-linking to soluble IL-13R α or urinary IL-13BP. Densitometric analysis of these data demonstrates that half-maximal inhibition of binding to soluble IL-13R α occurred with approximately 100 ng/ml IL-13, a 40-
5 fold higher concentration than required to inhibit fifty percent of the cross-linking to the Mr 55,000 dalton urinary IL-13BP.

The structural relationship between soluble IL-13R α and the Mr 55,000 dalton urinary IL-13BP was examined by cross-linking ^{125}I -IL-13 to both proteins and isolating the resultant complexes.
10 Each complex was then subject to exhaustive deglycosylation using N-glycosidase F and digestion with various concentrations of V8 protease. The products of these treatments were then resolved by SDS-polyacrylamide gel electrophoresis. The untreated and deglycosylated complex of IL-13 and the soluble ^{125}I -IL-13 appeared larger than the corresponding complex with the urinary IL-13BP. In addition, the products of V8 proteolysis of the two complexes
15 were clearly different, emphasising the structural difference between the IL-13R α and the Mr 55,000 dalton urinary IL-13BP.

A polyclonal antisera to the IL-13R α was raised in rabbits. This antisera was capable of immunoprecipitating the cross-linked product of ^{125}I -IL-13 with IL-13R α , while no
20 immunoprecipitation was observed with a pre-immune rabbit sera. Immunoprecipitation of the complex was not inhibited by the FLAG peptide but was inhibited by an excess of IL-13R α . In contrast to the IL-13R complex, the complex between the Mr 55,000 dalton urinary IL-13BP and ^{125}I -IL-13 was not recognised by the rabbit antisera to IL-13R α suggesting that these proteins are antigenically, as well as structurally and functionally distinct.

25

Soluble receptors for a variety of cytokines have been described. In some cases these act to augment a biological response, while in other situations they may inhibit the biological effect. In order to determine whether the purified soluble IL-13R α or the urinary IL-13BP could influence an IL-13 response, the inventors examined their effects on peritoneal macrophages.
30 Figure 3 demonstrates that although both the urinary IL-13BP and soluble recombinant IL-13R α can inhibit the binding of IL-13 to cell surface receptors expressed by macrophages, IL-

- 35 -

13BP is more efficient.

The purification of IL-13BP from mouse urine was shown following SDS-PAGE. The IL-13BP was purified on an IL-13 affinity column and then applied to a RP-HPLC column. The protein was eluted with a gradient of increasing acetonitrile. Each fraction was examined by SDS-PAGE and autoradiography. The results illustrated a silver-stained band with an apparent molecular mass of approximately 45,000 daltons which co-fractionates and is of a similar size to the IL-13BP detected by cross linking.

10

EXAMPLE 10 CLONING OF MURINE IL-13BP

The partial amino sequence of purified murine IL-13BP is determined. N-terminal, C-terminal and/or internal sequence is generally used. These data are used to generate oligonucleotide probes or primers to clone out the murine IL-13BP. Alternative cloning protocols include screening for murine IL-13BP expression using anti-IL-13BP antibodies. A variety of murine cell lines may be used as a source of IL-13BP DNA.

20

EXAMPLE 11 CLONING OF HUMAN IL-13BP

Methods similar to those in Example 10 are used to clone the human IL-13BP gene. Alternative methods include cross hybridization using the murine IL-13BP nucleotide sequence. A variety of human cell lines may be used as a source of human IL-13BP DNA.

25

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EXAMPLE 12

N-TERMINAL AMINO ACID SEQUENCE

The IL-13BP isolated according to Example 8 was subjected to N-terminal amino acid
5 sequencing and the sequence is set forth substantially as follows:

EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1].

More particularly the N-terminal sequence is EIKVNPPQDFEIXDPGLLGXYLYLQ
10 [SEQ ID NO:13].

Even more particularly the N-terminal sequence is EIKVNPPQDFEILDPGLLGXYLYLQ
[SEQ ID NO:21]

15

EXAMPLE 13

CLONING OF HUMAN IL-13BP

The N-terminal amino acid sequence of murine IL-13BP (Example 12) was used to scan
gene/EST databases.

20

In EST R52795, the region of homology with murine IL-13BP appeared to be C-terminal of
an initiation methionine residue which was followed by a putative signal sequence, at the end
of which was a canonical von Heijne signal sequence cleavage point. The region of homology,
therefore, occurred at the beginning of the mature coding region, consistent with the EST
25 encoding a secreted protein that was the human homologue of the murine IL-13BP.
Additionally, the N-terminal amino acid sequence of the mouse IL-13BP shared significant
homology with both the murine and human the IL-5 receptor α -chains, members of the
haemopoietin receptor family which are known to bind to four-alpha helical cytokines such as
IL-13.

30

The nucleotide sequence of R52795 (see SEQ ID NO:5, encodes N-terminal region of IL-

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13BP) was obtained by sequencing the 5' end of a cDNA clone from a human infant brain library. The clone number was YG99F10. The 3' end of this clone was also sequenced. Translation of SEQ ID NO:5 in each of three reading frames is shown in SEQ ID NOs. 6, 7 and 8, respectively. Referring to SEQ ID NO:5, a region identical to murine IL-13BP N-terminal amino acid sequence is the amino acid sequence EIKVNPPQDFEIXDPGXLGYYLQ [SEQ ID NO:1] which is in SEQ ID NO:6 and begins at nucleotide 211 and ends at nucleotide 282 of SEQ ID NO:5. A possible initiator methionine can be seen at nucleotide 127 of SEQ ID NO:5 and a putative signal sequence follows with the amino acid sequence in SEQ ID NO:6 of:

10 AFVCLAIGCLYTFLISTTFGCTSSS [SEQ ID NO:14].

The putative signal sequence cleaving point would be between S and D at nucleotide positions 202 to 207. The three putative amino acid translations given at SEQ ID NOs:6-8 have been translated from nucleotide 1, 5 and 3 of SEQ ID NO:5, respectively.

15

These results indicate that the IL-13BP is a member of the haemopoietin receptor family and, moreover, provides a means of cloning the cDNA using oligonucleotides designed from the 5' and 3' ESTs of clone YG99F10. An example of suitable oligonucleotides is 5' ATGGCTTTCGTTTGCTTGGCTATC3' [SEQ ID NO:2] nucl 127-150 of R52795 and 20 5'CAACATTCGCAAGAAAAATTCAGTTTATT3' [SEQ ID NO:3] nucl 12-40 of R52796.

The nucleotide sequence of R52796 is shown in SEQ ID NO:9 (encoding C-terminal region of IL-13BP) and three putative translations in different reading frames are shown in SEQ ID NOs: 10, 11 and 12, respectively. The reading frame showing a WSXWS motif is shown in SEQ ID NO:12 (nucleotides 171-185). The three putative reading frames given in SEQ ID 25 NOs: 10-12 have been translated from nucleotides 1, 2 and 3, respectively of SEQ ID NO:9.

The cloning product (eg. PCR product) is cloned into a mammalian expression vector such as pEF-BOS (Mizushima and Nagata, 1990), and the ability of the clone to encode the IL-13BP tested by transfection into COS cells and testing the ability of transfected cells to bind IL-13 with high affinity.

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EXAMPLE 14

CLONING OF FULL LENGTH HUMAN IL-13BP

The EST YG99F10 was obtained from ATCC and sequenced in full.

5

PCR was carried out on the ATCC plasmid using the following primers, with conventional conditions.

FORWARD 5' ATGCGGCGCGCCAGGAGATAAAAGTTAACCCT 3' [SEQ ID NO:15]
10 REVERSE 5' AGCTACGCGTTCAACGTAGCAAAGTTTTCTTCGATAG3' [SEQ ID NO:16]

The resultant product was digested with Asc I and Mlu I and cloned into the Mlu I site of pEF/FLAG/IL-3SS to yield a cDNA encoding the mouse IL-3 signal sequence, an N-terminal FLAG epitope tag and the mature extracellular domain (EIKVNP...to..KKTLLR) of human IL-
15 13BP. This nucleotide sequence and corresponding amino acid sequence is shown in SEQ ID NO:17. The amino acid sequence alone is shown in SEQ ID NO:18.

With reference to SEQ ID NO:17, the amino acid sequence from residue 1 (Met) to residue 33 (Gln) comprises the initiating methionine and signal sequence of murine IL-3. The Flag epitope
20 sequence follows (DYKDDDK-[SEQ ID NO:4]) and then the sequence of the mature IL-13 BP in which transcription has been terminated prior to the transmembrane domain to generate a soluble form.

Those skilled in the art will appreciate that the invention described herein is susceptible to
25 variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(US only) NICOLA, Nocos Antony, HILTON Douglas James, ZHANG Jian-Guo and
SIMPSON, Richard John

(ii) TITLE OF INVENTION: THERAPEUTIC MOLECULES

(iii) NUMBER OF SEQUENCES: 22

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(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Xaa Asp
 5 10

Pro Gly Xaa Leu Gly Tyr Leu Tyr Leu Gln
15 20

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGGCTTTCG TTTGCTTGGC TATC

24

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CAACATTCGC AAGAAAAATT CAGTTTATT

29

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Asp Tyr Lys Asp Asp Asp Asp Lys
5

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 473 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTAAGAACAC TCTCGTGAGT nCTAACGGTC TTCCGGATGA AGGCTATTG AAGTCGCCAT	60
AACCTGGTCA GAAGTGTGCC TGTCGGCGGG GAGAGAGGCA ATATCAAGGT TTAAATCTC	120
GGAGAAATGG CTTTCGTTTG CTTGGCTATC GGATGCTTAT ATACCTTTCT GATAAGCACA	180
ACATTTGGCT GTACTTCATC TTCAGACACC GAGATAAAAG TTAACCCTCC TCAGGATTTT	240
GAGATAGTGG ATCCCGGATA CTTAGGTTAT CTCTATTTGC AATGGCAACC CCCACTGTCT	300
CTGGATCATT TTAAGGAATG CACAGTGGA TATGAATAA AATACCGAAA CATTGGTAGT	360
GAAACATGGG AAGGACCATC ATTACTAAGA ATCTACATTT ACAAAGGATG GGGTTTGGAT	420
CnTTAACAAG GGGCATTGAA GGCGAAGGTT ACACACGGTT TTTACCCTGG GGC	473

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 157 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 1-471 of SEQ ID NO:5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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```

Val Arg Thr Leu Ser * Xaa Leu Thr Val Phe Arg Met Lys Ala Ile
 1              5              10              15

* Ser Arg His Asn Leu Val Arg Ser Val Pro Val Gly Gly Glu Arg
      20              25              30

Gly Asn Ile Lys Val Leu Asn Leu Gly Glu Met Ala Phe Val Cys Leu
      35              40              45

Ala Ile Gly Cys Leu Tyr Thr Phe Leu Ile Ser Thr Thr Phe Gly Cys
      50              55              60

Thr Ser Ser Ser Asp Thr Glu Ile Lys Val Asn Pro Pro Gln Asp Phe
 65              70              75              80

Glu Ile Val Asp Pro Gly Tyr Leu Gly Tyr Leu Tyr Leu Gln Trp Gln
      85              90              95

Pro Pro Leu Ser Leu Asp His Phe Lys Glu Cys Thr Val Glu Tyr Glu
      100              105              110

Leu Lys Tyr Arg Asn Ile Gly Ser Glu Thr Trp Glu Gly Pro Ser Leu
      115              120              125

Leu Arg Ile Tyr Ile Tyr Lys Gly Trp Gly Leu Asp Xaa * Gln Gly
      130              135              140

Ala Leu Lys Ala Lys Val Thr His Gly Phe Tyr Pro Gly
      145              150              155

```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 156 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 5-473 of SEQ ID NO:5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```

Glu His Ser Arg Glu Xaa * Arg Ser Ser Gly * Arg Leu Phe Glu
 1              5              10              15

Val Ala Ile Thr Trp Ser Glu Val Cys Leu Ser Ala Gly Arg Glu Ala
      20              25              30

Ile Ser Arg Phe * Ile Ser Glu Lys Trp Leu Ser Phe Ala Trp Leu
      35              40              45

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Ser Asp Ala Tyr Ile Pro Phe * * Ala Gln His Leu Ala Val Leu
   50                               55                               60

His Leu Gln Thr Pro Arg * Lys Leu Thr Leu Leu Arg Ile Leu Arg
   65                               70                               75                               80

* Trp Ile Pro Asp Thr * Val Ile Ser Ile Cys Asn Gly Asn Pro
                               85                               90                               95

His Cys Leu Trp Ile Ile Leu Arg Asn Ala Gln Trp Asn Met Asn *
                               100                               105                               110

Asn Thr Glu Thr Leu Val Val Lys His Gly Lys Asp His His Tyr *
   115                               120                               125

Glu Ser Thr Phe Thr Lys Asp Gly Val Trp Ile Xaa Asn Lys Gly His
   130                               135                               140

* Arg Arg Arg Leu His Thr Val Phe Thr Leu Gly
145                               150                               155

```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 157 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 3-473 of SEQ ID NO:5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

Lys Asn Thr Leu Val Ser Xaa Asn Gly Leu Pro Asp Glu Gly Tyr Leu
  1                               5                               10                               15

Lys Ser Pro * Pro Gly Gln Lys Cys Ala Cys Arg Arg Gly Glu Arg
   20                               25                               30

Gln Tyr Gln Gly Phe Lys Ser Arg Arg Asn Gly Phe Arg Leu Leu Gly
   35                               40                               45

Tyr Arg Met Leu Ile Tyr Leu Ser Asp Lys His Asn Ile Trp Leu Tyr
   50                               55                               60

Phe Ile Phe Arg His Arg Asp Lys Ser * Pro Ser Ser Gly Phe *
   65                               70                               75                               80

Asp Ser Gly Ser Arg Ile Leu Arg Leu Ser Leu Phe Ala Met Ala Thr
                               85                               90                               95

Pro Thr Val Ser Gly Ser Phe * Gly Met His Ser Gly Ile * Thr
   100                               105                               110

```

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Lys Ile Pro Lys His Trp * * Asn Met Gly Arg Thr Ile Ile Thr
 115 120 125

Lys Asn Leu His Leu Gln Arg Met Gly Phe Gly Xaa Leu Thr Arg Gly
 130 135 140

Ile Glu Gly Glu Gly Tyr Thr Arg Phe Leu Pro Trp Gly
 145 150 155

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..465

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

GGTGTTTTGG ATTATGGAAA TTGGnGACCA GAGAAGATGG ATACCTACCT TGGTGACTGC      60
CTACAGTTGA AAATGAAACA TACACCCTTG AAAACAACAA ATGAAACCCG ACAATTATGC      120

CTTTGTAGTA AGAAGCAAAG TGAATATTTA TTGCCTCAGA TGACGGAATT TGGAGTGAGT      180
GGAGTGATAA ACAATGCTGG GAAGGTGAAG ACCTATCGAA GAAACTTTG CCTACGTTTC      240
TGGCTACCAT TTGGTTTCAT CTTAATATTA GTTATATTTG TAACCGGTCT GCTTTTGCGT      300
AAGCCAAACA CCTACCCAAA AATGATTCCA GAATTTTCT GTGATACATG AAGACTTTCC      360
ATATCAAGAG ACATGGTATT GACTCAACAG TTTCCAGTCA TGGCCAAATG TTCAAATAA      420
GTCTCAATAA ACTGAATTTT TCTTGCGAAT GTTGAAAAAA AAAAA      465

```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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Ile Tyr Cys Leu Arg  *  Arg Asn Leu Glu  *  Val Glu  *  *  Thr
   50                      55                      60

Met Leu Gly Arg  *  Arg Pro Ile Glu Glu Asn Phe Ala Tyr Val Ser
   65                      70                      75                      80

Gly Tyr His Leu Val Ser Ser  *  Tyr  *  Leu Tyr Leu  *  Pro Val
                      85                      90                      95

Cys Phe Cys Val Ser Gln Thr Pro Thr Gln Lys  *  Phe Gln Asn Phe
                      100                      105                      110

Ser Val Ile His Glu Asp Phe Pro Tyr Gln Glu Thr Trp Tyr  *  Leu
   115                      120                      125

Asn Ser Phe Gln Ser Trp Pro Asn Val Gln Asn Lys Ser Gln  *  Thr
   130                      135                      140

Glu Phe Phe Leu Arg Met Leu Lys Lys Lys
   145                      150

```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 154 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE: CDS, nucleotides 3-464 of SEQ ID NO:9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```

Cys Phe Gly Leu Trp Lys Leu Xaa Thr Arg Glu Asp Gly Tyr Leu Pro
  1                      5                      10                      15

Trp  *  Leu Pro Thr Val Glu Asn Glu Thr Tyr Thr Leu Glu Asn Asn
          20                      25                      30

Lys  *  Asn Pro Thr Ile Met Pro Leu  *  *  Glu Ala Lys  *  Ile
          35                      40                      45

Phe Ile Ala Ser Asp Asp Gly Ile Trp Ser Glu Trp Ser Asp Lys Gln
   50                      55                      60

Cys Trp Glu Gly Glu Asp Leu Ser Lys Lys Thr Leu Pro Thr Phe Leu
   65                      70                      75                      80

Ala Thr Ile Trp Phe His Leu Asn Ile Ser Tyr Ile Cys Asn Arg Ser
          85                      90                      95

Ala Phe Ala  *  Ala Lys His Leu Pro Lys Asn Asp Ser Arg Ile Phe
          100                      105                      110

```

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Leu * Tyr Met Lys Thr Phe His Ile Lys Arg His Gly Ile Asp Ser
 115 120 125

Thr Val Ser Ser His Gly Gln Met Phe Lys Ile Ser Leu Asn Lys Leu
 130 135 140

Asn Phe Ser Cys Glu Cys * Lys Lys Lys
 145 150

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Xaa Asp Pro Gly Leu Leu Gly
 5 10 15

Tyr Leu Tyr Leu Gln
 20

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ala Phe Val Cys Lys Ala Ile Gly Cys Leu Tyr Thr Phe Leu Ile Ser Thr Thr Phe
 5 10 15

Gly Cys Thr Ser Ser Ser
 20 25

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATGCGGCGCG CCAGGAGATA AAAGTTAACC CT

32

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 37 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

AGCTACGCGT TCAACGTAGC AAAGTTTTCT TCGATAG

37

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1080 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1080

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

ATG GTT CTT GCC AGC TCT ACC ACC AGC ATC CAC ACC ATG CTG CTC CTG	48
Met Val Leu Ala Ser Ser Thr Thr Ser Ile His Thr Met Leu Leu Leu	
1 5 10 15	
CTC CTG ATG CTC TTC CAC CTG GGA CTC CAA GCT TCA ATC TCG GCG CGC	96
Leu Leu Met Leu Phe His Leu Gly Leu Gln Ala Ser Ile Ser Ala Arg	
20 25 30	
CAG GAC TAC AAG GAC GAC GAT GAC AAG ACG CGC CAG GAG ATA AAA GTT	144
Gln Asp Tyr Lys Asp Asp Asp Asp Lys Thr Arg Gln Glu Ile Lys Val	
35 40 45	
AAC CCT CCT CAG GAT TTT GAG ATA GTG GAT CCC GGA TAC TTA GGT TAT	192

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Asn	Pro	Pro	Gln	Asp	Phe	Glu	Ile	Val	Asp	Pro	Gly	Tyr	Leu	Gly	Tyr		
50						55					60						
CTC	TAT	TTG	CAA	TGG	CAA	CCC	CCA	CTG	TCT	CTG	GAT	CAT	TTT	AAG	GAA		240
Leu	Tyr	Leu	Gln	Trp	Gln	Pro	Pro	Leu	Ser	Leu	Asp	His	Phe	Lys	Glu		
65					70				75						80		
TGC	ACA	GTG	GAA	TAT	GAA	CTA	AAA	TAC	CGA	AAC	ATT	GGT	AGT	GAA	ACA		288
Cys	Thr	Val	Glu	Tyr	Glu	Leu	Lys	Tyr	Arg	Asn	Ile	Gly	Ser	Glu	Thr		
			85						90					95			
TGG	AAG	ACC	ATC	ATT	ACT	AAG	AAT	CTA	CAT	TAC	AAA	GAT	GGG	TTT	GAT		336
Trp	Lys	Thr	Ile	Ile	Thr	Lys	Asn	Leu	His	Tyr	Lys	Asp	Gly	Phe	Asp		
			100					105					110				
CTT	AAC	AAG	GGC	ATT	GAA	GCG	AAG	ATA	CAC	ACG	CTT	TTA	CCA	TGG	CAA		384
Leu	Asn	Lys	Gly	Ile	Glu	Ala	Lys	Ile	His	Thr	Leu	Leu	Pro	Trp	Gln		
		115					120					125					
TGC	ACA	AAT	GGA	TCA	GAA	GTT	CAA	AGT	TCC	TGG	GCA	GAA	ACT	ACT	TAT		432
Cys	Thr	Asn	Gly	Ser	Glu	Val	Gln	Ser	Ser	Trp	Ala	Glu	Thr	Thr	Tyr		
	130					135					140						
TGG	ATA	TCA	CCA	CAA	GGA	ATT	CCA	GAA	ACT	AAA	GTT	CAG	GAT	ATG	GAT		480
Trp	Ile	Ser	Pro	Gln	Gly	Ile	Pro	Glu	Thr	Lys	Val	Gln	Asp	Met	Asp		
145					150					155				160			
TGC	GTA	TAT	TAC	AAT	TGG	CAA	TAT	TTA	CTC	TGT	TCT	TGG	AAA	CCT	GGC		528
Cys	Val	Tyr	Tyr	Asn	Trp	Gln	Tyr	Leu	Leu	Cys	Ser	Trp	Lys	Pro	Gly		
				165					170					175			
ATA	GGT	GTA	CTT	CTT	GAT	ACC	AAT	TAC	AAC	TTG	TTT	TAC	TGG	TAT	GAG		576
Ile	Gly	Val	Leu	Leu	Asp	Thr	Asn	Tyr	Asn	Leu	Phe	Tyr	Trp	Tyr	Glu		
			180					185					190				
GGC	TTG	GAT	CAT	GCA	TTA	CAG	TGT	GTT	GAT	TAC	ATC	AAG	GCT	GAT	GGA		624
Gly	Leu	Asp	His	Ala	Leu	Gln	Cys	Val	Asp	Tyr	Ile	Lys	Ala	Asp	Gly		
		195					200					205					
CAA	AAT	ATA	GGA	TGC	AGA	TTT	CCC	TAT	TTG	GAG	GCA	TCA	GAC	TAT	AAA		672
Gln	Asn	Ile	Gly	Cys	Arg	Phe	Pro	Tyr	Leu	Glu	Ala	Ser	Asp	Tyr	Lys		
	210					215					220						
GAT	TTC	TAT	ATT	TGT	GTT	AAT	GGA	TCA	TCA	GAG	AAC	AAG	CCT	ATC	AGA		720
Asp	Phe	Tyr	Ile	Cys	Val	Asn	Gly	Ser	Ser	Glu	Asn	Lys	Pro	Ile	Arg		
225					230					235				240			
TCC	AGT	TAT	TTC	ACT	TTT	CAG	CTT	CAA	AAT	ATA	GTT	AAA	CCT	TTG	CCG		768
Ser	Ser	Tyr	Phe	Thr	Phe	Gln	Leu	Gln	Asn	Ile	Val	Lys	Pro	Leu	Pro		
				245					250					255			
CCA	GTC	TAT	CTT	ACT	TTT	ACT	CGG	GAG	AGT	TCA	TGT	GAA	ATT	AAG	CTG		816
Pro	Val	Tyr	Leu	Thr	Phe	Thr	Arg	Glu	Ser	Ser	Cys	Glu	Ile	Lys	Leu		
			260					265					270				
AAA	TGG	AGC	ATA	CCT	TTG	GGA	CCT	ATT	CCA	GCA	AGG	TGT	TTT	GAT	TAT		864

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Lys	Trp	Ser	Ile	Pro	Leu	Gly	Pro	Ile	Pro	Ala	Arg	Cys	Phe	Asp	Tyr		
	275						280					285					
GAA	ATT	GAG	ATC	AGA	GAA	GAT	GAT	ACT	ACC	TTG	GTG	ACT	GCT	ACA	GTT		912
Glu	Ile	Glu	Ile	Arg	Glu	Asp	Asp	Thr	Thr	Leu	Val	Thr	Ala	Thr	Val		
	290					295				300							
GAA	AAT	GAA	ACA	TAC	ACC	TTG	AAA	ACA	ACA	AAT	GAA	ACC	CGA	CAA	TTA		960
Glu	Asn	Glu	Thr	Tyr	Thr	Leu	Lys	Thr	Thr	Asn	Glu	Thr	Arg	Gln	Leu		
305					310					315					320		
TGC	TTT	GTA	GTA	AGA	AGC	AAA	GTG	AAT	ATT	TAT	TGC	TCA	GAT	GAC	GGA		1008
Cys	Phe	Val	Val	Arg	Ser	Lys	Val	Asn	Ile	Tyr	Cys	Ser	Asp	Asp	Gly		
				325				330						335			
ATT	TGG	AGT	GAG	TGG	AGT	GAT	AAA	CAA	TGC	TGG	GAA	GGT	GAA	GAC	CTA		1056
Ile	Trp	Ser	Glu	Trp	Ser	Asp	Lys	Gln	Cys	Trp	Glu	Gly	Glu	Asp	Leu		
			340				345						350				
TCG	AAG	AAA	ACT	TTG	CTA	CGT	TG										1080
Ser	Lys	Lys	Thr	Leu	Leu	Arg											
		355				360											

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 359 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met	Val	Leu	Ala	Ser	Ser	Thr	Thr	Ser	Ile	His	Thr	Met	Leu	Leu	Leu		
1				5				10					15				
Leu	Leu	Met	Leu	Phe	His	Leu	Gly	Leu	Gln	Ala	Ser	Ile	Ser	Ala	Arg		
		20					25					30					
Gln	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys	Thr	Arg	Gln	Glu	Ile	Lys	Val		
	35				40						45						
Asn	Pro	Pro	Gln	Asp	Phe	Glu	Ile	Val	Asp	Pro	Gly	Tyr	Leu	Gly	Tyr		
	50				55					60							
Leu	Tyr	Leu	Gln	Trp	Gln	Pro	Pro	Leu	Ser	Leu	Asp	His	Phe	Lys	Glu		
	65			70				75							80		
Cys	Thr	Val	Glu	Tyr	Glu	Leu	Lys	Tyr	Arg	Asn	Ile	Gly	Ser	Glu	Thr		
		85						90						95			
Trp	Lys	Thr	Ile	Ile	Thr	Lys	Asn	Leu	His	Tyr	Lys	Asp	Gly	Phe	Asp		
		100					105						110				

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Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu Leu Pro Trp Gln
 115 120 125
 Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala Glu Thr Thr Tyr
 130 135 140
 Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val Gln Asp Met Asp
 145 150 155 160
 Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser Trp Lys Pro Gly
 165 170 175
 Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe Tyr Trp Tyr Glu
 180 185 190
 Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile Lys Ala Asp Gly
 195 200 205
 Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala Ser Asp Tyr Lys
 210 215 220
 Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn Lys Pro Ile Arg
 225 230 235 240
 Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val Lys Pro Leu Pro
 245 250 255
 Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys Glu Ile Lys Leu
 260 265 270
 Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg Cys Phe Asp Tyr
 275 280 285
 Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val Thr Ala Thr Val
 290 295 300
 Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu Thr Arg Gln Leu
 305 310 315 320
 Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys Ser Asp Asp Gly
 325 330 335
 Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu Gly Glu Asp Leu
 340 345 350
 Ser Lys Lys Thr Leu Leu Arg
 355

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 948 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..948

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAG ATA AAA GTT AAC CCT CCT CAG GAT TTT GAG ATA GTG GAT CCC GGA	48
Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly	
1 5 10 15	
TAC TTA GGT TAT CTC TAT TTG CAA TGG CAA CCC CCA CTG TCT CTG GAT	96
Tyr Leu Gly Tyr Leu Tyr Leu Gln Trp Gln Pro Pro Leu Ser Leu Asp	
20 25 30	
CAT TTT AAG GAA TGC ACA GTG GAA TAT GAA CTA AAA TAC CGA AAC ATT	144
His Phe Lys Glu Cys Thr Val Glu Tyr Glu Leu Lys Tyr Arg Asn Ile	
35 40 45	
GGT AGT GAA ACA TGG AAG ACC ATC ATT ACT AAG AAT CTA CAT TAC AAA	192
Gly Ser Glu Thr Trp Lys Thr Ile Ile Thr Lys Asn Leu His Tyr Lys	
50 55 60	
GAT GGG TTT GAT CTT AAC AAG GGC ATT GAA GCG AAG ATA CAC ACG CTT	240
Asp Gly Phe Asp Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu	
65 70 75 80	
TTA CCA TGG CAA TGC ACA AAT GGA TCA GAA GTT CAA AGT TCC TGG GCA	288
Leu Pro Trp Gln Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala	
85 90 95	
GAA ACT ACT TAT TGG ATA TCA CCA CAA GGA ATT CCA GAA ACT AAA GTT	336
Glu Thr Thr Tyr Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val	
100 105 110	
CAG GAT ATG GAT TGC GTA TAT TAC AAT TGG CAA TAT TTA CTC TGT TCT	384
Gln Asp Met Asp Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser	
115 120 125	
TGG AAA CCT GGC ATA GGT GTA CTT CTT GAT ACC AAT TAC AAC TTG TTT	432
Trp Lys Pro Gly Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe	
130 135 140	
TAC TGG TAT GAG GGC TTG GAT CAT GCA TTA CAG TGT GTT GAT TAC ATC	480
Tyr Trp Tyr Glu Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile	
145 150 155 160	
AAG GCT GAT GGA CAA AAT ATA GGA TGC AGA TTT CCC TAT TTG GAG GCA	528
Lys Ala Asp Gly Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala	
165 170 175	
TCA GAC TAT AAA GAT TTC TAT ATT TGT GTT AAT GGA TCA TCA GAG AAC	576
Ser Asp Tyr Lys Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn	

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180	185	190	
AAG CCT ATC AGA TCC AGT TAT TTC ACT TTT CAG CTT CAA AAT ATA GTT			624
Lys Pro Ile Arg Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val			
195	200	205	
AAA CCT TTG CCG CCA GTC TAT CTT ACT TTT ACT CGG GAG AGT TCA TGT			672
Lys Pro Leu Pro Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys			
210	215	220	
GAA ATT AAG CTG AAA TGG AGC ATA CCT TTG GGA CCT ATT CCA GCA AGG			720
Glu Ile Lys Leu Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg			
225	230	235	240
TGT TTT GAT TAT GAA ATT GAG ATC AGA GAA GAT GAT ACT ACC TTG GTG			768
Cys Phe Asp Tyr Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val			
245	250	255	
ACT GCT ACA GTT GAA AAT GAA ACA TAC ACC TTG AAA ACA ACA AAT GAA			816
Thr Ala Thr Val Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu			
260	265	270	
ACC CGA CAA TTA TGC TTT GTA GTA AGA AGC AAA GTG AAT ATT TAT TGC			864
Thr Arg Gln Leu Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys			
275	280	285	
TCA GAT GAC GGA ATT TGG AGT GAG TGG AGT GAT AAA CAA TGC TGG GAA			912
Ser Asp Asp Gly Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu			
290	295	300	
GGT GAA GAC CTA TCG AAG AAA ACT TTG CTA CGT TG			948
Gly Glu Asp Leu Ser Lys Lys Thr Leu Leu Arg			
305	310	315	

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 315 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Glu	Ile	Lys	Val	Asn	Pro	Pro	Gln	Asp	Phe	Glu	Ile	Val	Asp	Pro	Gly
1				5					10					15	
Tyr	Leu	Gly	Tyr	Leu	Tyr	Leu	Gln	Trp	Gln	Pro	Pro	Leu	Ser	Leu	Asp
		20					25						30		
His	Phe	Lys	Glu	Cys	Thr	Val	Glu	Tyr	Glu	Leu	Lys	Tyr	Arg	Asn	Ile
		35					40					45			
Gly	Ser	Glu	Thr	Trp	Lys	Thr	Ile	Ile	Thr	Lys	Asn	Leu	His	Tyr	Lys

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50		55		60
Asp Gly Phe Asp Leu Asn Lys Gly Ile Glu Ala Lys Ile His Thr Leu				
65		70		75
80				
Leu Pro Trp Gln Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala				
	85		90	
95				
Glu Thr Thr Tyr Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val				
	100		105	
110				
Gln Asp Met Asp Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser				
	115		120	
125				
Trp Lys Pro Gly Ile Gly Val Leu Leu Asp Thr Asn Tyr Asn Leu Phe				
	130		135	
140				
Tyr Trp Tyr Glu Gly Leu Asp His Ala Leu Gln Cys Val Asp Tyr Ile				
	145		150	
155				
160				
Lys Ala Asp Gly Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala				
	165		170	
175				
Ser Asp Tyr Lys Asp Phe Tyr Ile Cys Val Asn Gly Ser Ser Glu Asn				
	180		185	
190				
Lys Pro Ile Arg Ser Ser Tyr Phe Thr Phe Gln Leu Gln Asn Ile Val				
	195		200	
205				
Lys Pro Leu Pro Pro Val Tyr Leu Thr Phe Thr Arg Glu Ser Ser Cys				
	210		215	
220				
Glu Ile Lys Leu Lys Trp Ser Ile Pro Leu Gly Pro Ile Pro Ala Arg				
	225		230	
235				
240				
Cys Phe Asp Tyr Glu Ile Glu Ile Arg Glu Asp Asp Thr Thr Leu Val				
	245		250	
255				
Thr Ala Thr Val Glu Asn Glu Thr Tyr Thr Leu Lys Thr Thr Asn Glu				
	260		265	
270				
Thr Arg Gln Leu Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys				
	275		280	
285				
Ser Asp Asp Gly Ile Trp Ser Glu Trp Ser Asp Lys Gln Cys Trp Glu				
	290		295	
300				
Gly Glu Asp Leu Ser Lys Lys Thr Leu Leu Arg				
	305		310	
315				

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Leu Asp Pro Gly Leu Leu Gly
5 10 15
Tyr Leu Tyr Leu Gln
20

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Glu Ile Lys Val Asn Pro Pro Gln Asp Phe Glu Ile Val Asp Pro Gly Tyr Leu Gly
5 10 15
Tyr Leu Tyr Leu Gln
20

CLAIMS:

1. An isolated proteinaceous molecule or a recombinant or synthetic form thereof capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13R α .
2. An isolated proteinaceous molecule according to claim 1 having a molecular weight in its native soluble form as determined by SDS-PAGE of from about 40,000 daltons to about 60,000 daltons.
3. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.
4. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGXYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.
5. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.
6. An isolated proteinaceous molecule according to claim 2 comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGXYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.
7. An isolated proteinaceous molecule according to claim 2 or 3 or 4 or 5 comprising an N-terminal amino acid sequence set forth in one of SEQ ID NO:6 or 7 or 8.
8. An isolated proteinaceous molecule according to claim 2 or 3 or 4 or 5 comprising a C-terminal amino acid sequence set forth in one of SEQ ID NO:10 or 11 or 12.

9. An isolated proteinaceous molecule according to claim 6 comprising an amino acid sequence set forth in SEQ ID NO:20.
10. An isolated proteinaceous molecule according to any one of claims 2 to 6 encoded by a nucleotide sequence substantially as set forth in SEQ ID NO:5 or SEQ ID NO:9 or SEQ ID NO:19 or a nucleotide sequence having at least about 50% similarity thereto and which is capable of hybridising thereto under low stringency conditions at 42°C.
11. An isolated nucleic acid molecule comprising a sequence of nucleotides which encodes or is complementary to a sequence which encodes a proteinaceous molecule capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13R α .
12. An isolated nucleic acid molecule according to claim 11 wherein said encoded proteinaceous molecule in its native form has a molecular weight of from about 40,000 daltons to about 60,000 daltons as determined by SDS-PAGE.
13. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.
14. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGXYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.
15. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEILDPLLGXYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.
16. An isolated nucleic acid molecule according to claim 12 comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGXYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

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17. An isolated nucleic acid molecule according to claim 13 or 14 or 15 or 16 encoding an N-terminal amino acid sequence set forth in at least one of SEQ ID NO:6 or 7 or 8 or an amino acid sequence having at least 50% similarity to one of SEQ ID NO:6 or 7 or 8.
18. An isolated nucleic acid molecule according to claim 13 or 14 or 15 or 16 encoding a C-terminal amino acid sequence as set forth in at least one of SEQ ID NO:10 or 11 or 12.
19. An isolated nucleic acid molecule according to claim 16 encoding an amino acid sequence as set forth in SEQ ID NO:20.
20. An isolated nucleic acid molecule according to claim 11 comprising a nucleotide sequence substantially as set forth in SEQ ID NO:5 or 9 or 19 or a nucleotide sequence having at least about 50% similarity thereto and which is capable of hybridising thereto under low stringency conditions at 42°C.
21. An expression vector comprising a promoter operably linked to a nucleic acid molecule as defined in any one of claims 11 to 20.
22. A method for purifying IL-13BP or its derivatives from a biological sample including body fluid or cell culture medium, said method comprising contacting said biological sample with immobilised IL-13 or an IL-13/IL-4 hybrid or a binding derivative thereof for a time and under conditions sufficient for a complex to form between said IL-13 and its binding protein, eluting said IL-13BP or IL-13/IL-4 from the immobilised IL-13 and collecting said eluted IL-13BP or IL-13/IL-4.
23. A peptide having first and second portions wherein one of said first and second portions is IL-13BP or a functional derivative thereof and the other of said first and second portions is IL-4BP or a functional derivative thereof wherein said polypeptide is capable of modulating biological processes involving IL-13 and/or IL-4.
24. A polypeptide according to claim 23 comprising the amino acid sequence

EIKVNPPQDFEIXDPGXLGYLYLQ [SEQ ID NO:1] or a derivative, homologue or analogue thereof.

25. A polypeptide according to claim 23 comprising the amino acid sequence EIKVNPPQDFEIXDPGLLGYLYLQ [SEQ ID NO:13] or a derivative, homologue or analogue thereof.

26. A polypeptide according to claim 23 comprising the amino acid sequence EIKVNPPQDFEILDPGLLGYLYLQ [SEQ ID NO:21] or a derivative, homologue or analogue thereof.

27. A polypeptide according to claim 23 comprising the amino acid sequence EIKVNPPQDFEIVDPGYLGYLYLQ [SEQ ID NO:22] or a derivative, homologue or analogue thereof.

28. A polypeptide according to claim 23 comprising an amino acid sequence of one of SEQ ID NO:6 or 7 or 8.

29. A polypeptide according to claim 23 comprising an amino acid sequence of one of SEQ ID NO:10 or 11 or 12.

30. A polypeptide according to claim 23 comprising the amino acid sequence set forth in SEQ ID NO:20.

31. A method of treatment comprising administering to a patient an IL-13 antagonising effective amount of an IL-13BP or its derivative for a time and under conditions sufficient to antagonise at least one property of IL-13.

32. A method according to claim 31 wherein the treatment is for an allergic reaction.

33. A composition comprising a proteinaceous molecule according to any one of claims

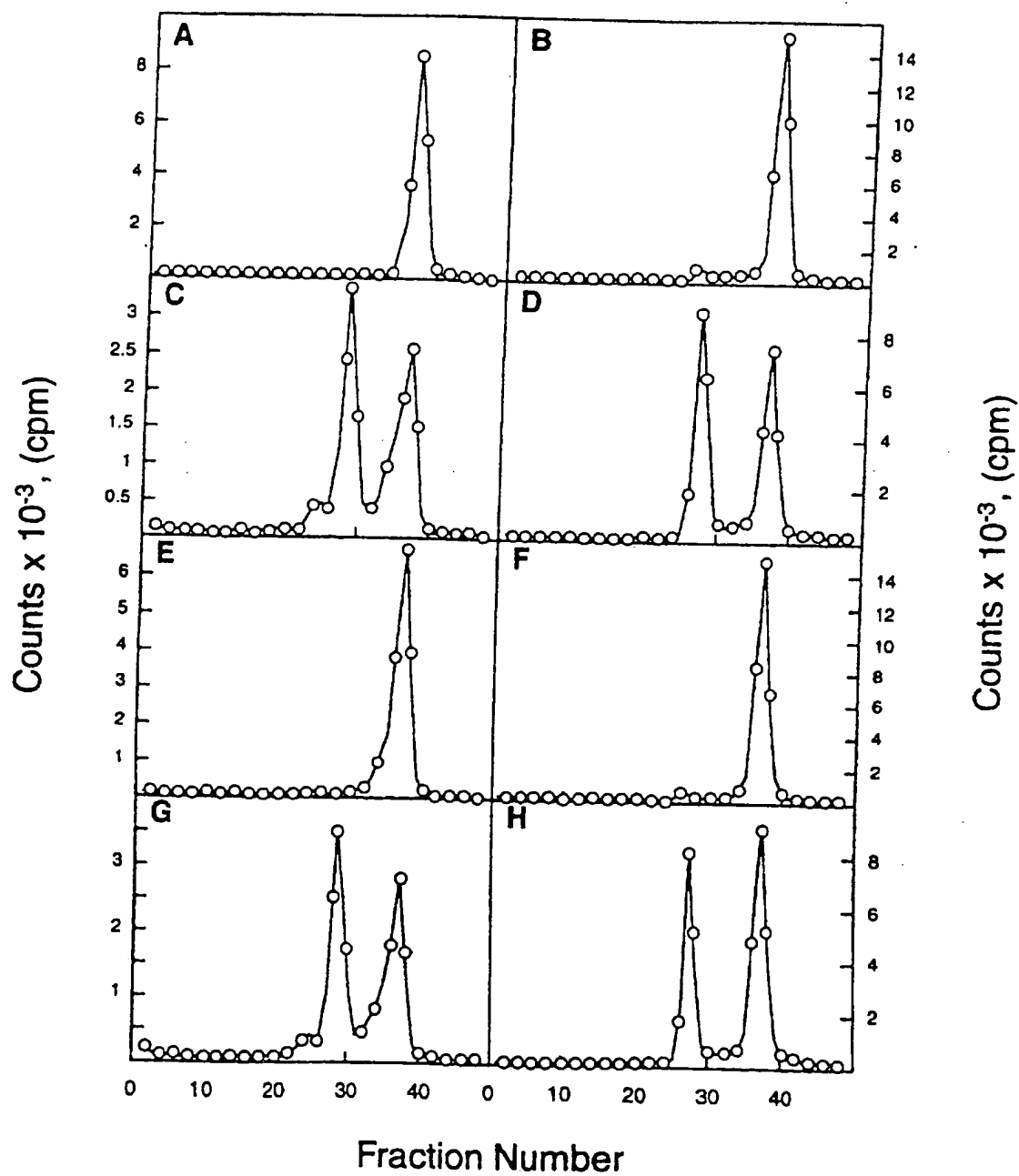
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1 to 10 and one or more pharmaceutically acceptable carriers and/or diluents.

- 34. An antibody to a proteinaceous molecule according to any one of claims 1 to 10.
- 35. An antibody according to claim 34 wherein the antibody is a monoclonal antibody.
- 36. A transgenic animal comprising a mutation in at least one allele of the gene encoding IL-13BP.
- 37. A transgenic animal according to claim 36 comprising a mutation in two alleles of the gene encoding IL-13BP.
- 38. A transgenic animal according to claim 36 or 37 wherein said animal is a murine animal.

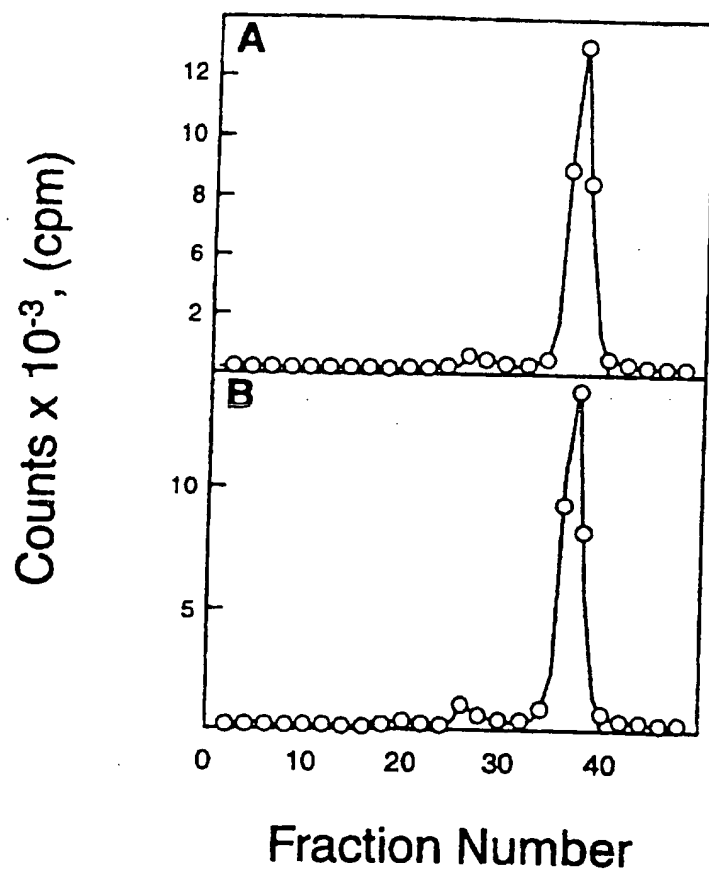
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FIGURE 1



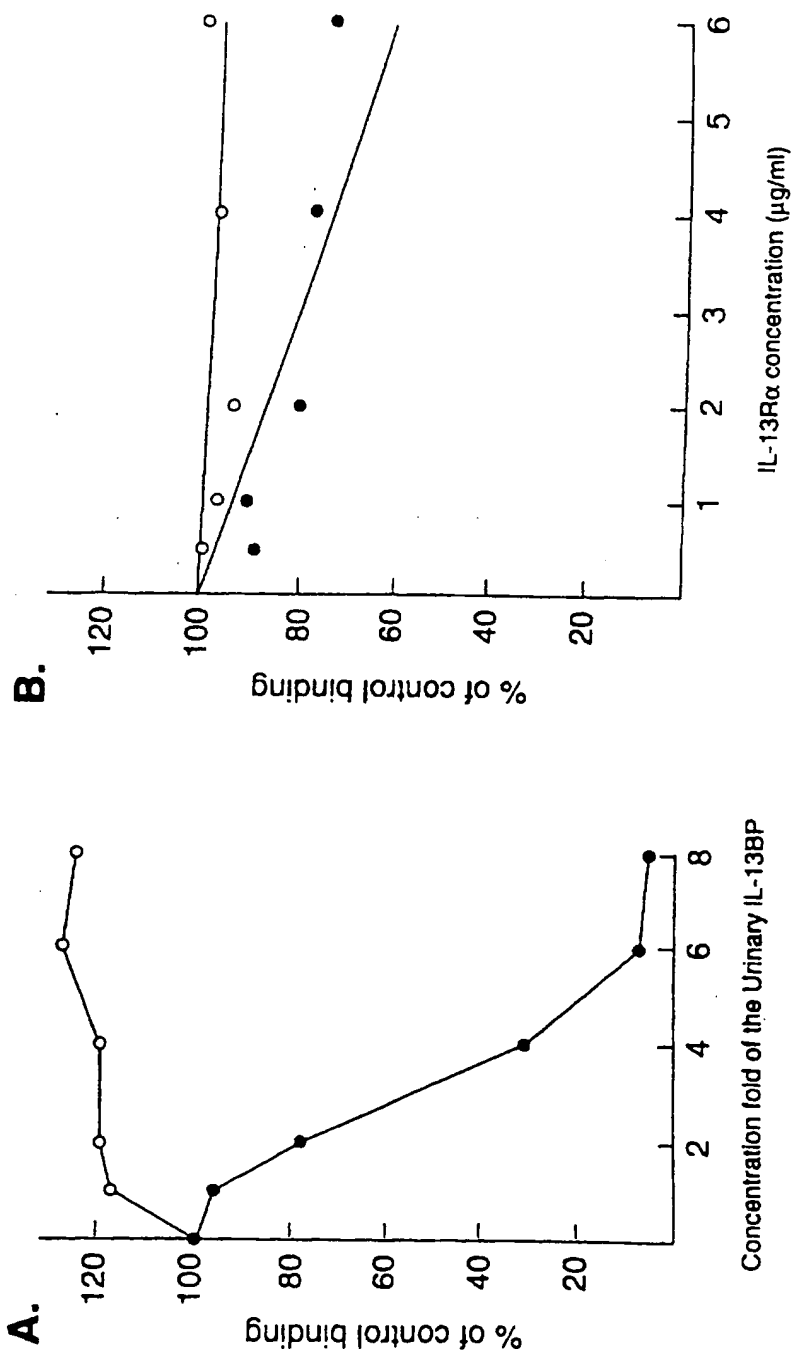
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FIGURE 2



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FIGURE 3



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU97/00591

A. CLASSIFICATION OF SUBJECT MATTER		
Int Cl ⁶ : A01K 67/00, 67/027, A61K 38/17, C07K 14/47, 16/18, C12N 15/12, 15/63		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) WPAT Derwent Database; Chemical Abstracts - Keywords below		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Medline - Keywords below, EMBL, GENE BANK, SWISS Prot, PIR		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPAT, Chemical Abstracts, Medline - Keywords: IL, interleukin, 13, 13BP, 13R, 4, 4BP, 4R, bind, antag, antibod, recept; EMBL, GENE BANK, SWISS Prot, PIR - Sequence Search: SEQ ID NOS 1, 7, 8, 10, 12, 13, 21, 22		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Immunology, volume 87, number 4, 1996, Bost et al., "In vivo treatment with anti-interleukin-13 antibodies significantly reduces the humoral immune response against an oral immunogen in mice", pages 633-641.	1, 2, 31
X	WO, 94/04680(Schering Corporation) 3 March 1994	1, 2, 31
P,X	WO, 97/20926(SANOFI) 12 June 1997	1-22, 31-35
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 29 October 1997		Date of mailing of the international search report 30 OCT 1997
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer CHRISTOPHER LUTON Telephone No.: (02) 6283 2256

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU97/00591

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	European Journal of Immunology, volume 27, number 4, 1997, Gauchat et al., "A novel 4-kb interleukin-13 receptor α mRNA expressed in human B, T, and endothelial cells encoding an alternate type-II interleukin-4/interleukin-13 receptor", pages 971-978.	1-22, 31-35
P,X	The Journal of Biological Chemistry, volume 272, number 14, 1997, Zhang et al., "Identification, Purification, and Characterization of a Soluble Interleukin (IL)-13-binding Protein", pages 9474-9480.	1-22, 31-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU97/00591

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO	94/04680	JP	7508179
		US	5596072
		EP	656947
WO	97/20926	AU	75760/96
		FR	2742156
END OF ANNEX			